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Use of doxycycline-controlled gene expression to reversibly alter milk-protein composition in transgenic mice.

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A reverse tetracycline transactivator-encoding cDNA under the control of the mammary specific beta-lactoglobulin promoter was linked to a bovine alpha-lactalbumin transcription unit driven by a reverse tetracycline-controlled transactivator/doxycycline-inducible human cytomegalovirus promoter. The construct was microinjected into eggs from alpha-lactalbumin-deficient mice. These mice produce a highly viscous lactose-free milk and have a shortened lactation period. Mice from three out of the nine transgenic lines investigated expressed reverse tetracycline-controlled transactivator mRNA in their lactating mammary glands at levels detectable by Northern analysis. Following doxycycline addition to the drinking water, lactation was fully restored in animals from the three lines. Doxycycline removal resulted in a reversal of phenotype. The observed mammary-specific and high expression of the doxycycline inducible reporter gene (up to 5.2 mg of recombinant alpha-lactalbumin.mL⁻¹ of milk, i.e. up to 13-fold induction) opens up exciting prospects to use the tetracycline system to study the development and functioning of the mammary gland, and to control the production level of active pharmaceutical proteins in the milk of transgenic animals.

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